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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,303	04/21/2004	Ralph C. Budd	2317.001A	5666

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/829,303	BUDD ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears n the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/973,476.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply with sequence rule.

DETAILED ACTION

1. *Claims 1-21 are pending.*

2. Applicant's election of Group V, claim 21 in the reply filed on 11/12/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claim 21 drawn to a method of inhibiting the proliferation of peripheral blood lymphocytes comprising administering a caspase-8 inhibitor is under consideration in the instant application.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 04/06/1999. It is noted, however, that applicant has not filed a certified copy of the 19915465 application as required by 35 U.S.C. 119(b).

4. This application contains sequences disclosures on pages 5 and 6 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Applicant is reminded to amend the specification and the claims accordingly.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *in vitro* inhibiting the proliferation of peripheral blood lymphocytes comprising administering a caspase-8 inhibitor , does not reasonably provide **enablement** for a method of in vivo inhibiting the proliferation of peripheral blood lymphocytes comprising administering a caspase-8 inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.
The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses detailed *in vitro* assays of the ability of 3 caspase inhibitors YVAD-fmk, zVAD-fmk and IETD-fmk to inhibit proliferation of T cells stimulated with anti-CD3 antibodies (Example 1 and 2 of the Specification as filed). The specification does not adequately teach how to effectively in vivo inhibiting the proliferation of blood lymphocytes by administering an effective amount of any caspase-8 inhibitor. Moreover, no animals models were used to study the effectively of inhibiting proliferation of peripheral blood lymphocytes by administering an effective amount of any caspase-8 inhibitor. Since there is no animal model studies and data in the specification to show the effectively of inhibiting the proliferation of peripheral blood lymphocytes by administering an effective amount of any caspase-8 inhibitor, it is unpredictable how to correlate *in vitro* results with *in vivo* use. Feldman et al (Transplantation proceedings, 1998, Vol.30, pages 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al., further teach that in a chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway. Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge

in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans.

Moreover, since the method of inhibiting the proliferation of peripheral blood lymphocytes by administering an effective amount of any caspase-8 inhibitor can be species- and model-dependent (seeVan Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. Moreover, an effective protocol for the method of *in vivo* inhibiting the proliferation of peripheral blood lymphocytes is subject to a number of factors which enter the picture beyond simply the administration to the subject an effective amount of any caspase-8 inhibitor. Disclosure of the *in vitro* data that 3 caspase inhibitors i.e. YVAD-fmk, zVAD-fmk and IETD-fmk can inhibit proliferation of T cells stimulated with anti-CD3 antibodies (Example 1 and 2 of the Specification as filed) cannot alone support the predictability of the method of *in vivo* inhibiting the proliferation of peripheral blood lymphocytes by administering to the subject an effective amount of any caspase-8 inhibitor . Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

An effective protocol for the method of *in vivo* inhibiting the proliferation of peripheral blood lymphocytes by administering to the subject an effective amount of any caspase-8 inhibitor in the absence of *in vivo* clinical data are unpredictable for the following reasons: (1) the caspase-8 inhibitor may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation etc; (2) the the caspase-8 inhibitor may not reach the target area because, i.e. the caspase-8 inhibitor may not be able to cross the mucosa or the caspase-8 inhibitor may be adsorbed by fluids, cells and tissues where the caspase-8 inhibitor has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In addition, although Specification describes certain *in vitro* experiments, there is no correlation on this record between *in vitro* experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on *in vitro* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

"There is no evidence of record that experimental animal models have been developed in this area which would be predictive of human efficacy." Ex parte Balzarini, 21 USPQ2d 1892.

There must be a rigorous correlation of pharmacological activity between the disclosed in vitro utility and an in vivo utility to establish practical utility.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of inhibiting in vivo the proliferation of peripheral blood lymphocytes by administering an effective amount of any caspase-8 inhibitor in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claim 21 is rejected under 35 U.S.C. 102(a) as being anticipated by Alam et al (J Exp.Med, 1999, V.190, pages 1879-1890) or by Kennedy et al (J. Exp. Med. 1999, V.190, pages 1891-1895).

Alam et al., teach a method of inhibiting the proliferation of peripheral blood lymphocytes comprising administering an effective amount of a caspase –8 inhibitor , i.e. zVAD (see entire document, Abstract and page 1887, left column in particular).

Kennedy et al ., teach a method of inhibiting the proliferation of peripheral blood lymphocytes comprising administering an effective amount of a caspase –8 inhibitor , i.e. zVAD (see entire document, Abstract and page 1892, left column in particular).

The references teaching anticipates the claimed invention.

8. No claim is allowed.

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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